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In accordance w[i]th the Patents (Companies Re-registration) Rules 1982, if a [c]ompany named in this certificate and any accompanying doc[u]ments has re-registered under the Companies Act 19[8]5 with the same name as that with which it was registered [i]mmediately before re-registration save for the substitut[i]on as, or the inclusion as, the last part of the name o[f] the words "public limited company" or their equivalents [i]n Welsh, references to the name of the [c]ompany in this cer[t]ificate and any accompanying documents shall be treated as [r]eferences to the name with which it is so re-registered.

I[n] accordance with t[h]e rules, the words "public limited co[m]pany" may be repl[a]ced by p.l.c., plc, P.L.C. or PLC.

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Signed W.J. Russell

Dated 11 AUG 1994

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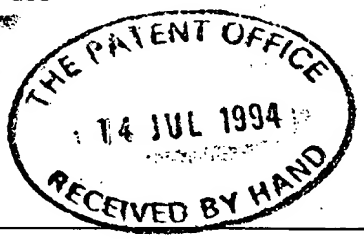

18JUL'94#00404355 PAT 1 77 UC 25.00

14 JUL 1994

Your reference 136420/2

9414192.6

Notes
Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071–438 4700).

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

The Patent Office — Request for grant of a Patent

Form 1/77

Patents Act 1977

❶ Title of invention

1 Please give the title of the invention: SYNTHESIS OF 17-(3-PYRIDYL) STEROIDS

❷ Applicant's details

❑ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name: BRITISH TECHNOLOGY GROUP LIMITED

Country *(and State of incorporation, if appropriate)*: U.K.

❷ Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases**, please give the following details:

Address: 101 NEWINGTON CAUSEWAY
LONDON

UK postcode *(if applicable)*: SE1 6BU

Country: U.K.

ADP number *(if known)*: 6095822001

Warning
After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977 and will inform the applicant if such prohibition or restriction is necessary. Applicants resident in the United Kingdom are also reminded that under Section 23, applications may not be filed abroad without written permission unless an application has been filed not less than 6 weeks previously in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction revoked.

2d, 2e and 2f: If there are further applicants please provide details on a separate sheet of paper.

☐ **Second applicant** ***(if any)***

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2f **In all cases**, please give the following details:

Address

UK postcode *(if applicable)*

Country

ADP number *(if known)*

❸ *An address for service in the United Kingdom must be supplied*

Please mark correct box

❸ Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ➡ ***go to 3b***

↓ ***please give details below***

Agent's name MR. R.K. PERCY, M.A. C.P.A.,

Agent's address BRITISH TECHNOLOGY GROUP LIMITED
101 NEWINGTON CAUSEWAY
LONDON

Postcode SE1 6BU

Agent's ADP number 40835 07003

3b: *If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.*

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

Address

Daytime telephone number *(if available)*

Postcode

ADP number *(if known)*

❹ Reference number

4 Agent's or applicant's reference number *(if applicable)* 136420/2

❺ Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No [X] ➡ ***go to 6***

⬇ ***please give details below***

❑ number of earlier application or patent number

❑ filing date

(day month year)

❑ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

❻ Declaration of priority

❻ If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day, month, year)*

❼ *The answer must be 'No' if:*
- *any applicant is not an inventor*
- *there is an inventor who is not an applicant,* ***or***
- *any applicant is a corporate body.*

❼ Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark correct box

Yes [ ] No [X] ➡ ***A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).***

❽ *Please supply duplicates of claim(s), abstract, description and drawing(s).*

❽ Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77	—		
Claim(s)	—	Description	7
Abstract	—	Drawing(s)	—

8b Which of the following documents also accompanies the application?

Please mark correct box(es)

Priority documents *(please state how many)*	—
Translation(s) of Priority documents *(please state how many)*	—
Patents Form 7/77 – Statement of Inventorship and Right to Grant *(please state how many)*	—
Patents Form 9/77 – Preliminary Examination/Search	—
Patents Form 10/77 – Request for Substantive Examination	—

❾ *You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.*

❾ Request

I/~~We~~ request the grant of a patent on the basis of this application.

Please sign here ➡

Signed Keith Percy R.K. PERCY Agent for the Applicant

Date 14th July 1994 ~~6TH JUNE 1994~~ (day month year) Mon.

A completed fee sheet should preferably accompany the fee.

Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to either:

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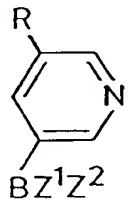
SYNTHESIS OF 17-(3-PYRIDYL) STEROIDS

Our U.K. Patent Application 9320132.5 entitled "SYNTHESIS OF 17-(3-PYRIDYL) STEROIDS" filed 30th September 1993, the entire contents of which are herein incorporated by reference, describes and claims a method of preparing a 3β-hydroxy- or 3β-(lower acyloxy) 16,17-ene-17-(3-pyridyl)-substituted steroid, wherein the 3β-(lower acyloxy) group of the steroid has from 2 to 4 carbon atoms, which comprises subjecting a 3β-hydroxy-16,17-ene-17-iodo or -bromo steroid to a palladium complex-catalysed cross-coupling reaction with a (3-pyridyl)-substituted borane, in which the pyridine ring is substituted at the 5-position by an alkyl group of 1 to 4 carbon atoms or is unsubstituted thereat, especially with a said borane of formula:



wherein R is a hydrogen atom or an alkyl group of 1-4 carbon atoms and Z^1 and Z^2 independently represent hydroxy or alkoxy or alkyl of 1-3 carbon atoms each or Z^1 and Z^2 together represent an alkylenedioxy group of 2 or 3 carbon atoms, in a proportion of from 1.0 to 1.2 equivalents of boron compound per equivalent of steroid, in an organic liquid, which is a solvent for the 3β-hydroxy steroidal reaction product, and optionally acylating the 3β-hydroxy reaction product.

The present patent application is directed to the following variants or improvements, considered separately or in any possible combination of two or more thereof (except where otherwise implied):

1. The proportion of organoboron compound to steroid is not critical provided that in the work-up of step (c), see below, a good solvent is used to keep the organoboron compound in solution especially diethyl ether or acetonitrile. In particular, it is believed that a proportion of at least 1.2 : 1 (equivalents) will reduce the amount of bis-steroidal by-product (see below). Preferably, therefore, it is in the range 1.2 : 1 to 1.5 : 1 (equivalents).

2. In the step of performing the palladium complex-catalysed cross-coupling reaction of the steroid with the organoboron compound, step (c), it is preferable to purge the reaction vessel with an inert gas, especially argon or nitrogen, to minimise the possibility of oxidation with a corresponding redox reduction of palladium to the metallic state.

3. Also in step (c), the yield can be improved by different work-up procedures, which may include crystallisation from acetonitrile/methanol. Acetonitrile is a preferred crystallisation solvent to keep boron compound as well as palladium compound in solution and is therefore used in an excess over methanol e.g. an excess of at least 5 : 1 and preferably about 8 : 1 by volume.

4. In the acetylation step (d), acetic anydride in pyridine solution is preferred as an acetylation agent.

5. In step (d), an impurity has been identified as a 16,17'-bis(steroidal) by-product. This could largely be removed by chromatography, but now that the by-product has been identified, those skilled in the art will be able more easily to identify solvents which will remove it, without the need for chromatography. Further, it is believed that with the higher organoboron : steroid ratios suggested above, the side-reaction leading to this impurity will be reduced.

6. The final product of step (d) may be crystallised direct from hexane, rather than from ethanol/water followed by hexane.

The following minor corrections are required to our Application 9320132.5:

1. At page 6 line 5, the ether removes the contaminating phosphine compounds, as well as the organoboron and palladium compounds already mentioned.

2. In Claim 3 at page 11 lines 30-32 cancel "R^{14} represents the residue of ..... alkyl group of 1-4 carbon atoms", to correct an obvious clerical error. R^{14} is as defined later in the claim, while R does not feature in claim 3 at all (only in claim 5).

3. In claim 8, the third organic liquid should be one in which the phosphine and palladium contaminants are more soluble than the steroidal reaction product.

The following Example illustrates the invention:

EXAMPLE

(a) Dehydroepiandrosterone-17-hydrazone

Into a 10 L round-bottomed flask, fitted with a magnetic stirrer bar, was placed dehydroepiandrosterone (288 g, 1.0 mol) and ethanol (5.0 L). To the resultant stirred solution was added hydrazine hydrate (195 ml, 4.0 mol), followed by a solution of hydrazine sulfate (0.65 g, 0.005 mol) in water (20 ml) [note: the hydrazine sulfate dissolved in this volume of water at ~ 40°C]. After stirring at room temperature for 5 days, water (4.5 L) was added, the mixture poured into water (10 L), and the white crystalline precipitate allowed to settle. The product was collected by filtration on a sinter, washed with cold water (2 x 500 ml), then with Et_2O (2 x 500 ml). The product was then dried in vacuo, firstly over silica gel, and finally over P_2O_5, to give the title compound as a white crystalline solid, mp 204-206°C (284.8g, 94%).

(b) 17-Iodo-androsta-5,16 dien-3β-ol

A 10 L round-bottomed flask, fitted with a magnetic stirrer bar, was charged with iodine (156.1 g, 0.615 mol), THF (4.0 L; GPR grade), and Et_2O (2.0 L; BDH specially dried grade). The resultant stirred solution was cooled by an ice/water bath to 0°C and 1,1,3,3-tetramethylguanidine (188 ml, 173 g, 1.50 mol) was added. A solution of dehydroepiandrosterone-17-hydrazone from step (a) (90.74 g, 0.30 mol) in THF (2.25 L) was then added slowly to the above iodine solution via a canula over about 2 h, whilst maintaining the reaction temperature at 0°C [note: N_2 is evolved as the hydrazine is added to the iodine solution]. After all the hydrazone solution was added, the mixture was stirred for an additional hour and the precipitate allowed to settle [note: a precipitate of tetramethylguanidium iodide forms during the reaction]. The mixture was then filtered, and the filtrate concentrated to an oil on a rotary evaporator.

This reaction was carried out a total of three times, thus using in total 272.22 g (0.90 mol) of dehydroepiandrosterone-17-hydrazone from step (a). The concentrated residues from the three separate reactions were combined and heated on an oil bath for 4 h, then allowed to cool [note: this converts any 17,17-diiodo by-product into the 17-vinyl iodide product]. This oil was then dissolved in Et_2O (5 L), filtered, and further diluted with additional Et_2O (4 L). The Et_2O solution was washed with aqueous HCl (1M; 3 x 500 ml) until the aqueous phase was acidic [note: the ether solution changes colour from brown to yellow when the aqueous phase remains acidified] then finally with water (500 ml). The Et_2O phase was separated, dried ($MgSO_4$), and concentrated to a volume of 3 L, then left to allow the product to crystallise. The yellow crystals were collected by filtration on a sinter, washed with hexane (3 x 500 ml) and dried under vacuum (335.4 g, 94%). Recrystallisation from ethanol-water (5:1) afforded the product as white crystals (297.3 g, 83%) mp 175-176°C, lit.[1] mp 173-174°C.

(c) 17-(3-Pyridyl)androsta-5,16-dien-3β-ol

In a 2 L round-bottomed flask, fitted with a magnetic stirrer bar, was placed the steroidal 17-iodo product from step (b) (98.0 g, 0.246 mol) and this was dissolved in THF (1.1 L). The flask was purged with argon and bis(triphenylphosphine)palladium (II) chloride catalyst (1.73 g, 0.0025 mol) was added, followed by diethyl(3-pyridyl)borane (43.35 g, 0.295 mol). To the resultant orange THF solution was added an aqueous solution of sodium carbonate (2M; 500 ml). The flask was fitted with a reflux condenser, and the apparatus purged again with argon. The mixture was then heated under reflux (~ 80°C) with stirring on a stirrer/heating mantle (Electrothermal MA) for 4 days [note: upon completion of the reaction the organic phase darkens in colour from orange to dark orange/brown] then allowed to cool.

This reaction was carried out a total of three times, thus using a total of 294.0 g (0.74 mol) of the steroidal 17-iodo product from step (b).

The reaction mixtures were combined and Et_2O (5 L) added. The organic phase was separated, washed with water (2 L), and left to give a first crop of crystals which were collected by filtration on a sinter. The filtrate was concentrated and the residue redissolved in Et_2O to afford a second crop of crystals. The aqueous phase and washings from the above work-up were extracted with hot toluene (2 L) on a steam bath and concentration of the toluene extracts afforded further product. The combined crude product from the above procedures was then dissolved in the minimum volume of hot methanol, filtered through a plug of "Celite" (Registered Trade Mark) and an equal volume of acetonitrile added to the methanol solution. The acetonitrile/methanol solution was then concentrated to half its original volume on a rotary evaporator and the solution left to crystallise. The resultant white crystals were collected by filtration on a sinter, washed with acetontrile and dried in

vacuo to constant weight (191.1 g, 74%), mp 202-212°C. A second recrystallisation from toluene-methanol (50:1) afforded the product as white crystals (146.8 g, 57%) mp 214-218°C, lit.[2] mp 228-229°C.

(d) 3β-Acetoxy-17-(3-pyridyl)androsta-5,16-diene

The following reaction was carried out in a 500 ml round-bottomed flask, fitted with a magnetic stirrer bar. To a suspension of the steroidal product from step (c) (26.5 g, 0.104 mol) in dry pyridine (200 ml), was added acetic anhydride (75 ml) and the mixture stirred at room temperature for 24 h. The pyridine and excess acetic anyhdride was removed on a rotary evaporator, initially with the water bath at 70°C, and finally at 80°C for 30 min. The resulting oil was dissolved in Et_2O (500 ml), washed with saturated acqueous $NaHCO_3$ (2 x 200 ml), dried (Na_2CO_3), and concentrated to an oil which crystallised on standing. ^{1}H-NMR spectroscopy at this stage showed the product contained about 5% of a 16,17'-bis(steroidal) contaminant, 3β-acetoxy-16-(3'β-acetoxyandrosta-5',16'-dien-17'-yl)-17-(3-pyridyl)androsta-5,16-diene, which originated as a by-product from the coupling reaction of step (c).

The product was therefore further purified by preparative flash chromatography using a 9 cm diameter column, with silica stationary phase (Merck 15111), eluting with dichloromethane. The by-product eluted first followed by the desired product, although the separation was incomplete. Fractions containing a significant amount of by-product were combined and subject to further chromatographic purification.

The foregoing reaction and purification procedure was carried out a total of four times, thus using a total of 146 g (0.418 mol) of the steroidal product from step (c).

The product-containing dichloromethane fractions from the chromatographic purification were concentrated and recrystallised from hexane to afford white crystals which were dried in vacuo to constant weight. The total amount of product obtained was 136.0 g (83%).

The dichloromethane fractions containing the least by-product were combined, and following recrystallisation from hexane, afforded the title compound as white cyrstals with mp 142-144°C (Lit[2] mp 144-145°C) which were reserved for the clinical trial (111 g). Analysis. Calculated: C,79.75; H, 8.50; N, 3.58. Found: C, 79.84; H, 8.55; N, 3.46. MS (m/z) : 392(M+1): 331(M-60). The IR spectrum showed a C=O band (3-acetate) at 1732 cm^{-1}. ^{1}H-NMR spectroscopic analysis showed that the material contained 0.9 mol % (1.5% w/w) of the bis(steroidal) by-product.

A second crop of white crystals of the product, containing about 3% w/w of bis(steroidal) by-product, was obtained and reserved for trial formulation (25 g).

A sample of the above-mentioned 16,17'-bis(steroidal) by-product was isolated as pale yellow crystals mp 269-270°C (from hexane) which is available for toxicological evaluation (4 g).

The spectroscopic data (NMR, IR and MS) of the final product from this procedure are consistent with its structure, and the NMR spectrum consistent with that reported for the product obtained from the small scale route previously described in reference [2]. The NMR spectrum of a 1:1 mixed sample of product from this route and from the route in reference [2] showed a single set of signals, thus verifying its identity.

References:

(1) D.H.R. Barton, G. Bashiardes and J. Fourrey, Tetrahedron, 44: 147-162 (1988).

(2) S.E. Barrie, M. Jarman and G.A. Potter, U.K. Patent Application Publication No. 2265624A.

BRITISH TECHNOLOGY GROUP Ltd

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Our Ref: 135279/UK/RKP/gbs

Mr R Honeywood
The Patent Office
Cardiff Road
NEWPORT
Gwent NP9 1RH

6 April 1994

Dear Mr Honeywood

PCT APPLICATION NO. PCT/GB 93/00531
BRITISH TECHNOLOGY GROUP LIMITED ET AL.

Thank you for the First Written Opinion and for so kindly discussing the objection by telephone with me. Your clarifying comments were most helpful.

AMENDMENT

Please replace pages 3, 13, 14, 21, 35 and 37 by the re-processed pages of the same number.

REMARKS

I have made the amendments previously requested, inserted in claim 1 a disclaimer of the 15α-epimer analogue of the 3β,15β-acetoxy-5,16-diene, removed from claim 1 the inappropriate disclaimer of 3β-ols and cancelled the "omnibus" claim 17. There are no other amendments. At this juncture, it is convenient to make a consolidated listing of the amendments and the reasons for them, so that it can be seen clearly how the original pages have been amended and that the amendments are correct and are justified.

1. Claim 1, line 24: Change "17-(3-pyridyl)androsta-5,14,16-trien-3β-ol and" to "3β-acetoxy-17-(3-pyridyl)androsta-5,14,16-triene,"

2. Claim 1, line 25: Cancel the whole of this line.

3. Claim 1, line 26: (a) Change "3-acetates" to "3β,15α- and 3β,15β-diacetoxy-17-(3-pyridyl)androsta-5,16-diene" ; (b) after "3β-methoxy-17-(3-pyridyl)" insert "-5α-".

4. Claim 17 : Cancel this claim.

5. Page 3, line 13 : Change "17-(3-pyridyl)androsta-5,14,16-trien-3β-ol" to "3β-acetoxy-17-(3-pyridyl)androsta-5,14,16-triene," ; delete "15α-".

Cont'd 2/...

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6. Page 3, line 14: Cancel the whole of this line.

7. Page 3, line 15: Change "3-acetates" to "3β,15α- and 3β,15β-diacetoxy-17-(3-pyridyl)androsta-5,16-diene.".

8. Page 3, line 19: Change "22" to "32" .

9. Page 3, line 21: After "3β-methoxy-17-(3-pyridyl)" insert "-5α-".

10. Page 13, line 9: Change "v" to "vi" .

11. Page 14, line 33: Change "s" to "S" .

12. Page 21, line 32: After "5.76", cancel "(1H,"

Amendments 1 and 5 correct an error in the disclaimer. The paper by J. Wicha and M. Masnyk, Bulletin of the Polish Academy of Sciences : Chemistry 33 (1-2), 19-27 (1985) discloses as compound (12) only the 3-acetate of 17-(3-pyridyl)androsta-5,14,16-trien-3β-ol, not the alcohol (3β-ol) itself. The same compound is that mentioned by J. Wicha et al., Heterocycles 20, 231-234 (1983), at page 234, footnote 7. (Compare the experimental section on page 24 of the 1985 paper with said footnote in the 1983 paper and note that the reaction conditions described are the same and the melting points given for the product similar).

Amendments 2 and 6 correct another error in the disclaimer. The same Wicha and Masnyk paper discloses only the 3-acetate of 15β-acetoxy-17-(3-pyridyl)androsta-5,16-dien-3β-ol, as compound (11), not the alcohol (3β-ol) itself. This alcohol is at present disclaimed in both claim 1 and page 3.

Amendments 2 and 6 also correct a third error and an inconsistency between the description and claim 1. At present, the description disclaims a 15α-acetoxy-3β-ol and its 3β-acetate. Claim 1, disclaims neither. In fact, the prior art discloses the 15α-acetoxy-3β-acetate, but not the corresponding 15α-acetoxy-3β-ol. The 15α-acetoxy-3β-acetate is compound (13) of the J. Wicha and M. Masnyk (1985) paper. The formula on page 21 is wrongly written as the 15β-acetoxy-3β-acetate and to understand that it is in fact the 15α-acetoxy-3β-acetate, one has to read the text on page 21 and also at page 22 lines 11-15. A 15α-acetoxy-3β-ol is not disclosed in the prior art cited. The amendments therefore disclaim only the 15α-acetoxy-3β-acetate, i.e. a 3β, 15α-diacetoxy compound.

Amendments 3(a) and 7 are consequential on the deletion of the 3β-ols from the disclaimer. They simply write out the 3-acetates by their systematic names.

These changes to the disclaimer do not introduce new subject matter, because the description makes clear at page 3 lines 10-12 that the disclaimer is of the compounds which are known as intermediates in the Wicha and Masnyk 1985 paper referred to.

Cont'd 3/...

Amendments 3(b) and 9 are for clarification, since the references mentioned at page 3 lines 18-22 relating to the "accidental" disclosure of one of the claimed compounds refer only to 5α-epimers.

Amendment 4 cancels the "omnibus" claim.

Amendments 8 and 10-12 relate to obvious typographical errors.

I enclose a copy of the correspondingly manuscript-amended pages for reference purposes.

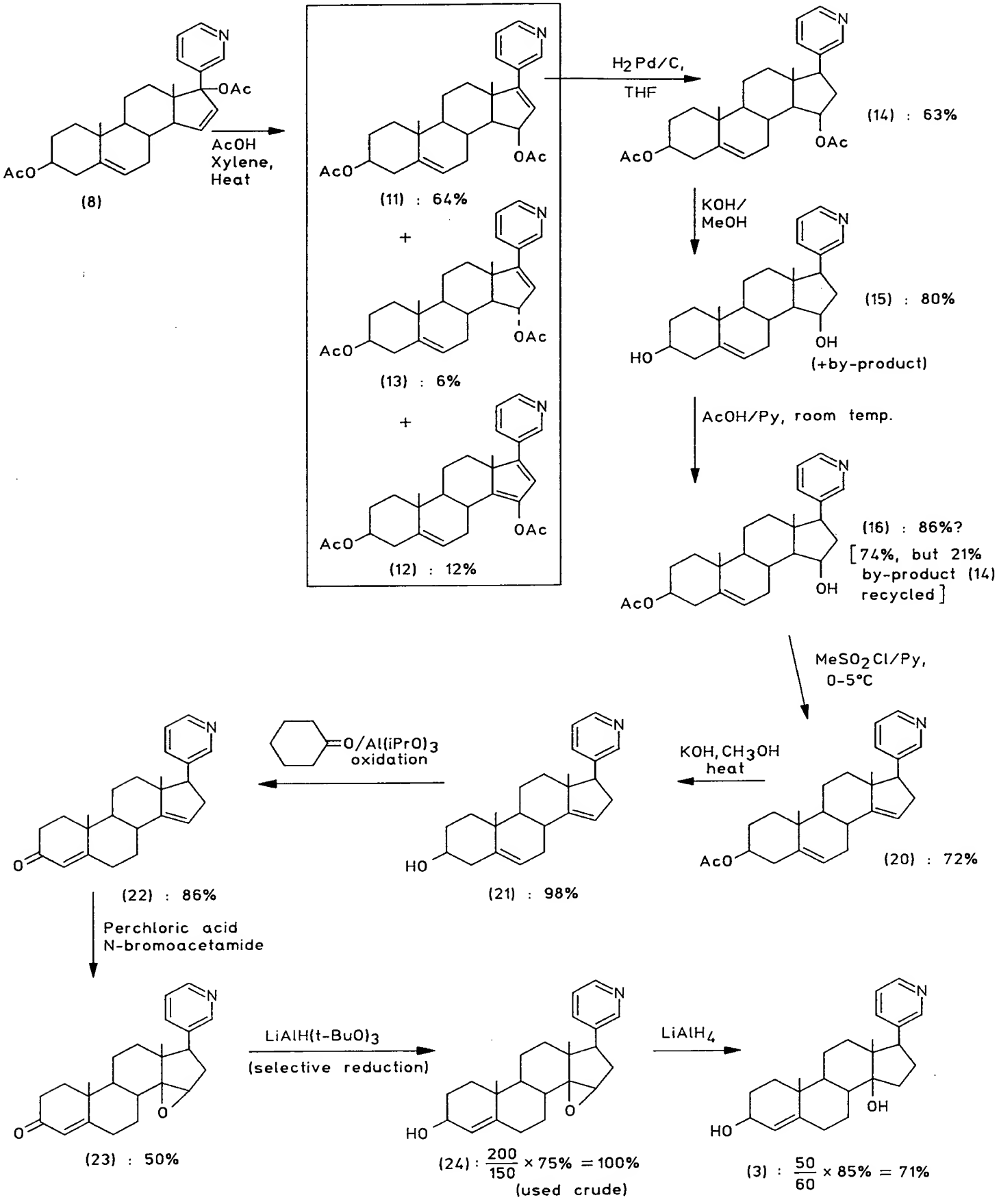
I believe that the application is now in good form for issue of a "clean" International Preliminary Examination Report raising no adverse citations and observations. If there is any point outstanding I would be grateful for a telephone call on extension 2311.

Yours sincerely

Keith Percy

R K PERCY
Chartered Patent Agent
Agent for the Applicant(s)

Enc: 1 copy new pages 3, 13, 14, 21, 35 & 37.
1 copy manuscript-amended pages



Overall yield approx.

$64 \times 63 \times 80 \times 86 \times 72 \times 98 \times 86 \times 50 \times 100 \times 71\% = 6.0\%$

08/315882

12

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

SUSAN E. BARRIE *ET AL.* Atty. Ref: **604-291**

Serial No. **Not yet known** Group:

Filed: Examiner:

For: **17-SUBSTITUTED STEROIDS USEFUL IN CANCER TREATMENT** Date:

* *

Honorable Commissioner of Patents
and Trademarks,
Washington D.C. 20231.

Dear Sir,

INFORMATION DISCLOSURE STATEMENT

REMARKS

Attached are a completed Form PTO 1449 listing references in connection with the present application, a copy of each of those references, together with a copy of an international search report which issued in the basic PCT international application number PCT/GB93/00531 and a copy of a letter dated April 6, 1994 relating to the PCT application. The last-mentioned item is provided in case it might be helpful when reading the Wicha *et al.* references, but the examiner is respectfully requested to check the statements made therein in case there should be any inadvertent error.

The examiner is requested to initial the attached PTO Form 1449 and return a copy of the initialed document to the undersigned as an indication that the references have been considered and made of record.

Respectfully submitted,
NIXON & VANDERHYE P.C.

By: _____
Leonard C. Mitchard
Reg. No. 29,009

1100 North Glebe Road,
8th Floor,
Arlington, VA 22201-4714,

Tel: 703-816-4000
Fax: 703-816-4100

Attachments: PTO Form 1449, listed references, letter and Search Report